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IN THE

Supreme Court of the United States

MYLAN INC., MYLAN LABORATORIES INC., MYLAN PHARMACEUTICALS INC. AND MATRIX LABORATORIES LTD.,

Petitioners,

v.

DAIICHI SANKYO COMPANY, LTD. AND DAIICHI SANKYO, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION

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QUESTION PRESENTED

Whether the Federal Circuit's common sense application of 35 U.S.C. § 103(a) in the context of new pharmaceutical compounds is in conflict with this Court's decision in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

STATEMENT PURSUANT TO RULE 29.6

Respondent Daiichi Sankyo, Inc. is a wholly owned subsidiary of Respondent Daiichi Sankyo Co., Ltd. Daiichi Sankyo Co., Ltd. has no parent company and no publicly traded company owns ten percent or more of the stock of Daiichi Sankyo Co., Ltd.

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COUNTERSTATEMENT OF THE CASE

Respondents Daiichi Sankyo Co., Ltd. and Daiichi Sankyo, Inc. ("Daiichi Sankyo") are the assignees of United States Patent No. 5,616,599 (the "'599 patent") covering the chemical compound olmesartan medoxomil, the active ingredient in Respondents' blockbuster BENICAR® family of medicines.[1] Respondents sued Petitioners Mylan Inc., Mylan Laboratories Inc., Mylan Pharmaceuticals Inc. and Matrix Laboratories Ltd. (collectively "Mylan"), for infringement of the '599 patent by Petitioners' proposed generic copies of the BENICAR® medicines. Petitioners admitted infringement. After trial, the United States District Court for the District of New Jersey held that Petitioners had not proven their one defense, that the '599 patent was invalid for obviousness. The United States Court of Appeals for the Federal Circuit affirmed.

The Petition begins with a list of diseases and conditions for which it asserts that there are no available generic treatments, in an apparent effort to persuade the Court that something is horribly wrong with the way the lower courts address pharmaceutical compound patents and that this Court must intervene to correct the situation. Petition at 2. Apart from the fact that the assertion is simply mistaken,[2] Petitioners ignore the reality that

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1. The BENICAR® family of medicines includes BENICAR® (active ingredient, olmesartan medoxomil) and two combination drugs, BENICAR HCT® and AZOR® (active ingredients, olmesartan medoxomil and additional compounds), all of which are indicated for the treatment of hypertension.

2. Many generic drugs are available for every one of the conditions the Petition lists and, in fact, Petitioners sell generic versions of thirty-three hypertension drugs, seven diabetes drugs, one epilepsy drug, and one osteoporosis drug.

were it not for the availability of strong patent protection for new pharmaceutical compounds there would be *no* treatments -- generic or otherwise -- available at *any* price for those and a long list of other ailments, for the simple reason that no one would invest the years of research and hundreds of millions (or even billions) of dollars necessary to discover, develop and bring to market the innovative new drug products upon which our very lives depend. Breathless policy arguments about the cost of healthcare do not convert a legally correct and intensely detailed, fact specific decision below into a case that satisfies the standards for a writ of certiorari and requires the attention of this Court.

Petitioners' central argument, which they never actually made in either of the courts below, is that the Federal Circuit is mistaken to begin the obviousness analysis in a pharmaceutical compound case by considering what lead compound or compounds a chemist of ordinary skill in the art would have looked to for inspiration as she or he began research to find a new and better drug. *See* Petition at 11. According to Petitioners, this "lead compound test" both frustrates the Congressional intent, reflected in the Hatch-Waxman Act,[3] to facilitate the marketing of generic drugs and constitutes a rigid and inflexible obviousness rule of the type this Court rejected in *KSR*.[4] Petition at 10, 18. Petitioners are mistaken on both counts.

First, while it is true that the Hatch-Waxman Act made it easier for generic drug companies to challenge

3. 21 U.S.C. § 355.

4. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

the patents of highly successful, blockbuster drugs, without the need to duplicate the extensive and expensive testing undertaken by the innovator, or to incur the risk of substantial damages if their challenges failed, the statute did not in any way change the substantive standards by which the validity of pharmaceutical compounds was to be judged. That is, Congress made it easier (and more attractive) for generic companies to test the validity of important pharmaceutical patents, but it chose not to do anything to change, much less dictate, the outcome of those cases. Nothing in the Federal Circuit's treatment of this case, or the others cited in the Petition, conflicts with the Hatch-Waxman Act in any way.

Second, there is nothing rigid or inflexible about beginning the analysis of obviousness in a pharmaceutical compound case by attempting to identify one or more lead compounds and then asking whether the person of ordinary skill in the art, typically a research chemist, would have had a reason to expect success by progressing down a logical path from that starting point to the ultimate compound that was the subject of the patent. As demonstrated by the record in this case, and in each of the cases discussed in the Petition, this inquiry is intensely factual in nature and turns on what the scientific knowledge at the time would have caused the skilled artisan to believe and to expect. This approach has the added benefit of faithfully reflecting the scientific process actually employed by those in the field -- as the expert witnesses on *both* sides agreed in this case -- whereby the researcher looking to discover a better drug of a particular type begins by studying the structure and properties of the most promising known compound(s) and then looks for possible modifications that might be expected to

produce something better. Far from being a rigid and inflexible test, this is simply an application to a particular field of scientific endeavor of precisely the common sense approach *KSR* requires. And the Federal Circuit has never precluded using other or different analyses if the facts warranted.

The alternative approach now advocated by Petitioners relies entirely upon hindsight -- something this Court's obviousness jurisprudence, including *KSR*, forbids. Rather than begin with the most promising known leads and ask where the skilled researcher would have been motivated to go from there, Petitioners start with the patented compound itself and then work backwards to identify the most structurally similar prior art and then argue that the differences are obvious. But the appropriate inquiry is not what may or may not appear obvious once the winning compound has been discovered -- even the most remarkable inventions can seem obvious after the fact. The question is whether, based on the prior art, one of ordinary skill would have found the invention obvious *before* it was made. Hindsight cannot help, but only hinders, the effort to answer that question.

In this case, either approach would produce the same outcome. As noted above, Petitioners never questioned the use of the lead compound analysis at trial or before the Federal Circuit. The parties disagreed as to which of the various prior art compounds would have been selected as leads by a medicinal chemist at the time, but everyone agreed that this was the appropriate framework for the obviousness analysis in this case. After a ten day trial, the district court held, in a well-reasoned and detailed opinion, that the lead compounds proposed by

Petitioners would not have been so viewed by a person of ordinary skill, but that even if they had been, that still would not have led to the discovery of olmesartan medoxomil. What Petitioners attempt to trivialize as a one atom structural difference between the patented compound and Petitioners' preferred lead compound, in fact dramatically changed the relevant characteristics of the molecule and did so in a way the prior art expressly taught against. The district court's detailed findings of fact, supported by voluminous scientific evidence which was largely undisputed and drawn from the testimony of witnesses on both sides, established that even crediting Petitioners' arguments concerning the appropriate lead compound, a person of ordinary skill in the art would not have expected olmesartan medoxomil to possess the qualities it does. After its own detailed review and based upon a well reasoned opinion, the Federal Circuit unanimously affirmed. Nothing in the record, the result or the contextually appropriate obviousness analysis employed by both courts below merits granting certiorari in this case.

1. Countless lives have been saved or extended by olmesartan medoxomil, the active ingredient in Respondents' pioneering BENICAR® family of anti-hypertensive medicines and the compound at issue in this case. (App.[5] 78a). Respondents discovered olmesartan medoxomil by pursuing a research path that ran contrary to the conventional wisdom in the field, including that of the two companies that conducted the earliest research in this area, Takeda and DuPont.

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5. "App." refers to the Appendix submitted with Mylan's Supreme Court Petition for a Writ of Certiorari.

Scientists still do not know the causes of hypertension. But, in the 1970s, they learned that the human renin-angiotensin system played a (little understood) role in regulating blood pressure, so scientists looked for chemical compounds to act on this system as a means of controlling hypertension. (App. 27a-28a). Takeda found the first angiotensin II receptor blockers ("ARBs"), but they were not active enough to use in humans. (App. 28a-29a).

Using the three best Takeda compounds as lead compounds, E.I. du Pont de Nemours Company, Inc. ("DuPont") embarked on its own development program, creating hundreds of new compounds and eventually discovering a compound effective enough for use in humans. (App. 29a). That compound, called "losartan," was considered a milestone in the field. (App. 30a-31a).[6]

DuPont's patent on losartan and its other publications taught that "lipophilic" structures were needed at the 4-position of the molecule for best activity. (App. 49a). Lipophilicity means an affinity for a fatty environment, as opposed to "hydrophilicity," which refers to an attraction to water. (App. 44a n.9). The relationship of lipophilicity and hydrophilicity can be described, in familiar terms, as "oil and water do not mix."

Notwithstanding the promise of losartan, DuPont continued to look for better ARBs. (App. 33a). At an important scientific meeting, DuPont announced its

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6. DuPont disclosed losartan, along with hundreds of related compounds, in United States Patent No. 5,138,069 ("the '069 patent"). (App. 31a). Following the expiration of the losartan patent, generic versions -- including one from Petitioners -- have been introduced into the market.

breakthrough second generation compound called DUP 532 -- which followed the teachings of the previous DuPont work to increase lipophilicity at the 4-position. (App. 48a). DuPont also synthesized a number of back-up compounds, which were never commercialized or featured in scientific meetings, and patented them in United States Patent No. 5,137,902 ("the '902 patent").[7] (App. 34a-35a). The '902 patent compounds followed DuPont's established teachings too and increased lipophilicity at the 4-position. (App. 48a).

At the same time, other pharmaceutical companies, including Merck, Ciba-Geigy, Eisai, and Takeda, developed their own "second generation" ARBs. (App. 36a-37a). They all had one structural feature in common -- they followed the DuPont teaching of lipophilicity at the 4-position. (App. 54a-55a). The published data on a number of these second generation compounds was more extensive than that of the '902 patent compounds and showed much more promising activity. (App. 59a-60a).

The Respondents' scientists forged a new path -- using insights from their unique testing methodology, they synthesized more than 700 compounds of a wide variety of structures, and eventually created olmesartan medoxomil. Olmesartan medoxomil has a hydrophilic group (a hydroxyisopropyl) at the 4-position -- the opposite of a lipophilic group that DuPont's work taught would

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7. The '902 patent did not issue until after Daiichi Sankyo had filed its olmesartan medoxomil patent application so the Daiichi Sankyo inventors could not possibly have known about it prior to their invention. But, the '902 patent is considered prior art because its application was filed two months before the olmesartan medoxomil patent application. (App. 59a n.13).

give the best activity. (App. 61a-62a). Also, olmesartan medoxomil has a medoxomil prodrug ester at the 5-position, unlike any of the DuPont work. (App. 64a). The overall structures of olmesartan medoxomil and the '902 patent compounds are significantly different. Based on the existing DuPont teachings, those in the field would have expected olmesartan medoxomil to be a failure -- but surprisingly it had 100 times the potency of losartan when orally administered. (App. 31a, 70a-71a).[8]

2. The '599 patent, covering olmesartan medoxomil, was issued to Respondent Daiichi Sankyo Co., Ltd. by the United States Patent and Trademark Office ("USPTO") on April 1, 1997. (App. 32a). During prosecution of the '599 patent, the USPTO examiner considered the two primary prior art references relied on by Petitioners at trial -- the DuPont '069 and '902 patents -- and decided that olmesartan medoxomil was novel and not obvious, based in part on olmesartan medoxomil's hydrophilic 4-position. (App. 62a).

3. The success of the BENICAR® family of medicines prompted Petitioners to submit several Abbreviated New Drug Applications ("ANDAs"), seeking approval to market generic olmesartan medoxomil products. (App. 39a). Along with their ANDAs, Petitioners filed certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) stating that their generic

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8. Seven ARBs are now on the market, including losartan and olmesartan medoxomil. (App. 37a-38a). Of these, olmesartan medoxomil is the only ARB with a hydrophilic group at the 4-position. And, research uncovered that olmesartan medoxomil binds to the angiotensin receptor in a different way than the other ARBs and has less drug interactions -- all due to its hydrophilic 4-position. (App. 76a, 74a).

products would not infringe any valid claim of the '599 patent. *Id.* In response to the Paragraph IV certifications, Respondents filed three actions in the United States District Court for the District of New Jersey, which were consolidated for trial. *Id.* Petitioners admitted that their generic olmesartan medoxomil products would infringe claim 13 of the '599 patent, and the only issue for trial was whether claim 13 was obvious over the prior art. (App. 26a). Specifically, Petitioners anchored their obviousness argument on a lead compound analysis -- that an ordinary chemist would have selected the DuPont '902 patent compounds as "lead compounds" and modified those compounds to derive olmesartan medoxomil. (App. 58a). Petitioners never advanced any other framework for the lower courts' analysis of obviousness, on which they bore the burden of proof.

4. Following a ten day bench trial, the district court rejected Petitioners' obviousness theory on all counts. (App. 10a-12a, 14a). The district court's 53-page opinion relied primarily on evidence from Petitioners' own witnesses and exhibits and made detailed factual findings on the four factors required by this Court's opinion in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966).[9] (App. 26a-84a).

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9. *Graham* explained that an obviousness inquiry is a matter of law, based on four general factual inquires:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the art in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject-matter is determined.

There was no substantive dispute below regarding the first *Graham* factor, the level of skill in the art. (App. 42a). The parties agreed and the district court held that the question of obviousness in this case should be judged from the perspective of a medicinal chemist with the ability to analyze structure-activity relationships. *Id.*

With respect to the second *Graham* factor, the "scope and content of the prior art," the district court found that "the prior art taught away from the use of a hydrophilic group at the 4-position of the imidazole ring." (App. 45a).

As to the third *Graham* factor, the "differences between the claimed subject matter and the prior art," the district court found, as a factual matter, that there are significant structural differences between olmesartan medoxomil and the '902 patent compounds. (App. 61a). For example, olmesartan medoxomil has a hydrophilic alcohol group at the 4-position, while the '902 patent compounds have lipophilic alkanes there. *Id.* These are known to chemists of skill in the art as very different functional groups with *opposite* properties as to lipophilicity, hydrogen bonding, and water solubility. (App. 62a). Although characterized repeatedly by Petitioners below -- and even in the Petition -- as a "minor" distinction consisting of only a single atom, the district court found as a factual matter that this difference is exceptionally significant and anything but "minor." *Id.* The district court also found a "significant difference" in structure at the 5-position. (App. 64a).

Graham, 383 U.S. at 17. Other objective indicia of non-obviousness, such as the "commercial success" of the patented compound, might also "give light to the circumstance surrounding the origin of the subject matter." *Graham*, 383 U.S. at 17-18; *KSR*, 550 U.S. at 406.

Continuing its analysis of the third *Graham* factor, the district court rejected, on three separate bases, Petitioners' contention that an ordinary artisan would have started with the '902 patent compounds and modified them to reach olmesartan medoxomil. First, the district court found that one of ordinary skill could have "selected a lead compound from a 'broad selection of compounds,'" and nothing pointed to the '902 patent compounds as a place to start. (App. 60a). Second, the district court found that even "[a]ssuming that the '902 patent compounds would have been selected as lead compounds," Petitioners failed to prove that an ordinary artisan would have modified the '902 patent compounds as necessary to obtain olmesartan medoxomil. (App. 64a-65a). Third, the district court found that a medicinal chemist of ordinary skill could not have reasonably expected success with such modifications. (App. 70a).

Finally, as to the fourth *Graham* factor, the objective indicia of non-obviousness, the district court found that these factors "further mitigate against a finding of obviousness." (App. 72a).

5. On appeal, Petitioners again advocated using a lead compound analysis, relying on the '902 patent compounds as leads to support a finding of obviousness. (App. 14a). Petitioners did not challenge the lead compound approach, but argued that it had not been applied properly by the district court, contending that the '902 patent compounds were lead compounds *per se* because, after olmesartan medoxomil was invented, the '902 patent compounds could be selected out of the extensive prior art as the structurally closest compounds. (App 17a). The Federal Circuit rejected this argument, noting that the proper

analysis "must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." *Id.* (emphasis in original). Petitioners also argued that "the prior art may point to more than a 'single lead compound for further development efforts.'" (App. 18a) (quoting *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). The Federal Circuit agreed that more than a single lead was possible, affirming the district court's finding that there were a number of promising leads, but that the '902 patent compounds were not among them, based on the many other compounds with superior properties known at the time. *Id.*

Finally, the Federal Circuit also found no error in the district court's finding that, even accepting the '902 patent compounds as leads, the prior art taught away from using the hydrophilic group found in olmesartan medoxomil. (App. 18a-19a). The Federal Circuit particularly noted the "single atom difference" that Petitioners again emphasize here, affirming that this change "is of greater significance than it superficially appears, as it is the difference between functional groups." (App. 22a n.4).

REASONS FOR DENYING THE PETITION

The Petition for a writ of certiorari does not raise any question that warrants review by this Court, and certainly none that was raised by Petitioners below.

A. The Lead Compound Analysis Is Simply a Common Sense Application of Traditional Obviousness Principles to the Research and Development of New Medicines

Contrary to the Petition, there is no rigid and inflexible "lead compound test" that permeates the Federal Circuit's jurisprudence in chemical compound cases. Rather, the lead compound analysis is simply one way in which the obviousness principles embodied in the patent statute and explained in *Graham* are applied in the specific context of pharmaceutical research and development. This common sense approach to the obviousness inquiry is entirely consistent with this Court's direction in *KSR*.

The lead compound framework simply applies the requirement of the patent statute that for an invention to be obvious, the differences between it and the prior art must be such that the "subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. The statute recognizes the basic truth that almost any invention, no matter how innovative at the time, will appear obvious when looking backward from the solution. *Expanded Metal Co. v. Bradford*, 214 U.S. 366, 381 (1909); *see also Krementz v. S. Cottle Co.*, 148 U.S. 556 (1893). Thus, the obviousness evaluation must be from the perspective of

"the time the invention was made," or in the words of this Court, the obviousness inquiry must "guard against slipping into use of hindsight." *Graham*, 383 U.S. at 36 (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (6th Cir. 1964)). And, the "as a whole" instruction of the statute prohibits a conclusion of obviousness because each component of an invention can be found in the prior art. There must have been an "apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. The inquiry must also be made from the vantage of those skilled in the field of the invention -- "a person having ordinary skill in the art." 35 U.S.C. § 103.

What Petitioners deride as a "lead compound test" is but a fact specific application of these principles using the language of medicinal chemistry, the art relevant in this case and others like it, and paralleling the way that medicinal chemistry research is actually done. Medicinal chemistry research often starts with a "lead compound" which is "a compound with known properties that a medicinal chemist uses as a starting point for drug development," as Petitioners' proffered medicinal chemistry expert testified at trial.[10] (App. 58a). That is, for a chemist seeking to make new, useful chemical compounds, the first step in research may be selecting a known prior art compound (or family of compounds) to modify. This selection may be very clear (*i.e.*, selecting the only known compound that works in a certain way). Or,

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10. While chemists often call a starting point compound a "lead compound," the terminology can differ. For example, the Amicus brief describes a process in which the chemist selects "candidate compounds" (*i.e.*, "lead compounds") and attempts to modify them. (Brief *Amicus Curiae* of Generic Pharmaceutical Association in Support of Petitioners at 16.)

the chemist may have a "broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda Chem. Indus., Ltd.. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007).[11]

The choice of known elements as starting points is not unique to medicinal chemistry; "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 550 U.S. at 418-419. For an invention to be found obvious, to protect against the "distortion caused by hindsight bias," there must be "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418-421. This analysis includes reasons to select the known elements as starting points. *Id.* at 420-26 (reason to select Asano as a starting point because it had a fixed pivot point, which was an "ideal mount for a sensor"); *see also United States v. Adams*, 383 U.S. 39 (1966) (finding no obviousness when there was no reason to use a particular starting point for modification) (cited approvingly in *KSR*). Then, the analysis looks to the proposed modifications in the context of the selected starting point. *KSR*, 550 U.S. at 424-425 (asking "whether a pedal designer of ordinary skill starting with Asano would have found it obvious to put the sensor on a fixed pivot point").

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11. The choice of starting point is carefully considered: "When selecting a lead point for development, a medicinal chemist of ordinary skill considers a multitude of factors, including the lead compound's potency." (Lipinski 4/20/09 Tr. JA 1582:12-19; Weinstock 3/31/09 Tr. JA 87:25-88:4.)" (App. 58a).

Thus, in the medicinal chemistry context, if a patent challenger relies on the modification of a known compound to demonstrate obviousness, the challenger must provide some reason that an ordinary medicinal chemist would prospectively select that known compound and make those modifications. Without this prospective reasoning, the obviousness analysis would devolve into a hindsight search of prior art for pieces of the invention, using the invention itself as a guide -- an approach prohibited by the patent statute and this Court's precedent. 35 U.S.C. § 103; *KSR*, 550 U.S. at 421; *Graham*, 383 U.S. at 36.

This analysis uses the chemistry term "lead compound," which reflects how chemists describe their research, but is not substantively different than the "known element" of *KSR*. That the Federal Circuit's decisions reflect the terminology used in the medicinal chemistry discipline is not surprising, given the patent statute's direction to apply the viewpoint of "a person having ordinary skill in the art." 35 U.S.C. § 103. But, for all inventions, regardless of differences in the technical terminology to parallel the research in each field, the essential obviousness inquiry remains the same. As this Court recognized in an analogous context (the determination of patent infringement under the doctrine of "equivalence") in *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, the "particular linguistic framework used is less important than whether the test is probative of the essential inquiry," and the "particular word choice" should not be "micromanag[ed]" by this Court but left to the "sound judgment" of the Federal Circuit in its "area of . . . expertise." 520 U.S. 17, 40 (1997). This Court explained further that "[d]ifferent linguistic frameworks may be more suitable to different cases, depending on

their particular facts" and "refinement" of the framework would take place on a "case-by-case" basis. *Id.* That holds equally true here.

In the real world of medicinal chemistry, the decisions of which starting point (or points) to choose and which modifications to make, have significant ramifications. Each starting point is susceptible to different potential modifications -- sometimes measured in the thousands -- and each modification may lead to very different results. In the end, the choices made by the medicinal chemist may lead to remarkable success or abject failure. In this case, the inventors made choices against the conventional wisdom, which nonetheless provided remarkable success. That the *ex post* analysis of whether success is truly innovative reflects how the research and development process actually works is neither formulaic nor rigid; it is common sense.

B. The Federal Circuit Decisions Cited by Petitioners Do Not Evidence a Rigid or Inflexible Test for Non-Obviousness of Chemical Compounds

Petitioners' dramatically-phrased "troubling pattern" of "nonobviousness in *each and every* chemical compound case since *KSR*" comprises but four cases before this one[12]

12. The so-called "pattern" includes: *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009); *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008); *Ortho-McNeil Pharm., Inc., v. Mylan Labs., Inc.*, 520 F.3d 1358 (Fed. Cir. 2008); and *Takeda*, 492 F.3d 1350. Petitioners also go further and call this a "long-standing pattern" of the Federal Circuit rejecting every challenge since the "enactment of the Hatch-Waxman Act," but, in the 25 years since the Hatch-Waxman

-- the "pattern" is arrived at only by selectively excluding decisions in cases involving non-pharmaceutical chemical compounds, other pharmaceutical inventions (including those related to salts, formulations, and methods of treatment), and the Federal Circuit's decision in *Altana*. Petition at 3, 12-13.

The excluded cases cut against the "pattern." For example, *Altana* is a pharmaceutical compound case in which the Federal Circuit engaged in the lead compound analysis and affirmed the district court's denial of a preliminary injunction based on a substantial question of obviousness. *Altana*, 566 F.3d at 1007.[13] (While excluded by Petitioners here, Petitioners told the Federal Circuit that *Altana* was a case "of particular importance." (Brief for Appellant at 24, 2009 WL 4088507 at 13, *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346 (Fed. Cir. 2010) (No. 2009-1511))). And, the "pattern" is broken by the many other cases involving pharmaceuticals which were analyzed under a similar "combination of known elements" framework, each tailored to the research challenges at issue, and found obvious.[14]

Act was enacted only two other such cases were decided by the Federal Circuit. *Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006) and *Yamanouchi Pharm. Co., Ltd., v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000).

13. Likewise, in *Novartis Pharm. Corp. v. Teva Pharm. USA, Inc.*, the Federal Circuit summarily affirmed a district court's denial of a preliminary injunction based on a substantial question of obviousness. 280 Fed. Appx. 996 (Fed. Cir. 2008) (affirming, without an opinion, 2007 WL 2669338 (D.N.J. 2007) (unpublished decision)).

14. The Federal Circuit's flexible approach is apparent from the whole body of pharmaceutical cases, where it has tailored the

According to the Petition, arguments of obviousness were rejected in the four previous chemical compound cases "for the sole reason that the lead compound test is impracticable to meet." Petition at 30. But, the semantics of the analysis did not dictate the results, the facts of those cases did. Two of the cases found no reason to begin with the "lead compound" proposed by the patent challenger. *Eisai*, 533 F.3d at 1358; *Takeda*, 492 F.3d at 1360. However, in all of Petitioners' cited cases, the Federal Circuit also assumed the choice of the starting point proposed by the patent challenger, but found no reason to modify the proposed lead compound in the manner the challenger suggested. *Proctor & Gamble*, 566 F.3d at 997; *Eisai*, 533 F.3d at 1359 ("no reasons a skilled artisan would have considered modification"); *Ortho-McNeil*, 520 F.3d at 1365; *Takeda*, 492 F.3d at 1360; *see also Eli Lilly*, 471 F.3d at 1379; *Yamanouchi*, 231 F.3d at 1345.

Further, half of the cases cited by Petitioners -- including this one -- found the prior art "taught away" from the combination. *See, e.g., Eisai*, 533 F.3d at 1358 (modification required "drop[ping] the very feature, the

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combination of known elements inquiry to the type of invention and research challenge at issue. For example, for salts, the inquiry has been in the context of known salts; for pharmaceutical formulations, the context is known formulation options, etc. Each approach mirrors how persons skilled in the art would actually view these different research challenges -- but the essential inquiry remains the same. *See, e.g., Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341,1350 (Fed. Cir. 2009); *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370-71 (Fed. Cir. 2003); *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997); as well as the cases cited in the Petition at 13.

fluorinated substituent, that gave this advantageous property"); *Takeda*, 492 F.3d at 1358 (the alleged starting point caused side effects); *see also Eli Lilly*, 471 F.3d at 1378 (quoting with approval the district court's finding that "the art as a whole teaches directly away"). Again, this is independent of any lead compound analysis -- *KSR* confirmed the long-held principle that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR*, 550 U.S. at 416.

Petitioners incorrectly criticize the Federal Circuit as "refusing" to consider the "obvious to try" rationale in the chemical compound cases. Petition at 27. *KSR* explained that being "obvious to try" may provide reasoning for the combination of elements: "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp" and "[i]f this leads to the anticipated success" the combination is "likely" obvious. *KSR*, 550 U.S. at 421. The Federal Circuit explicitly used the "obvious to try" rationale in the cited cases and affirmed factual findings that the inventions in those cases were not "obvious to try." *See, e.g., Procter & Gamble*, 566 F.3d at 997 ("In this case, there is no credible evidence that the structural modification was routine."); *Ortho-McNeil*, 520 F.3d at 1364 ("[T]his clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness."); *Takeda*, 492 F.3d at 1359-1360 (quoting *KSR*, and finding the modifications proposed were not "routine steps in the drug optimization process" thus "[t]he evidence showed that it was not obvious to try."). And, in *Altana*, which Petitioners' analysis ignores, the Federal

Circuit applied the lead compound analysis and affirmed the district court's conclusion that a substantial question of obviousness existed, in part, because "[d]efendants have raised a substantial question that this combination was at the least obvious to try . . . ." *Altana*, 566 F.3d at 1009.

These cases refute Petitioners' assertion that the Federal Circuit has "exclusively" applied the "lead compound test" as the "sole" method for determining obviousness of chemical compound patent claims. Petition at 3, 20; Amicus at 14. Instead, the Federal Circuit cases cited by Petitioners explain that this analysis is permissive and merely one option for proving obviousness. *See Altana*, 566 F.3d at 1007 (obviousness "*may be* proven by the identification of some motivation" to select and modify a known compound) (emphasis added); *Eisai*, 533 F.3d at 1357 ("Obviousness based on structural similarity thus *can be* proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.") (emphasis added) (internal citations omitted).[15]

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15. Petitioner's argument that the supposed "trend" is "further perpetuated by the PTO's [Patent Trademark Office's] adoption of the lead compound analysis in its 2010 PTO Guidelines for patent examiners" is wrong. Petition at 21. The Patent Office Guidelines set forth seven examples of flexible rationales which may be used to analyze obviousness. Although Petitioner argues that "most of the chemical compound cases appear under the lead compound analysis" in the Guidelines, *none* of the seven rationales is a "lead compound analysis." Rather, just as described herein, chemical compound cases are discussed under a "known elements" rationale. Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex, 75 FR 53643-01 (Sept. 1, 2010) (example 4.11).

Indeed, in the cases cited by Petitioners, as in this case, it was the patent challengers who sought to meet their burden of proving obviousness by focusing on a particular lead compound and possible modifications. *See, e.g., Eisai*, 533 F.3d at 1358-59 ("Teva alone selected lansoprazole as the anchor for its obviousness theory, not the district court."); *Takeda*, 492 F.3d at 1357 and n.3 ("By 'lead compound,' we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify" and the court would "use Alphapharm's terminology of 'lead compound' in this opinion, deciding the appeal as it has been argued."); *see also Yamanouchi*, 21 F. Supp. 2d at 372 (describing "Schein's basic argument" as the selection of a lead compound and steps to modify it to derive the invention).

Finally, to the extent Petitioners suggest a systemic bias on the part of the Federal Circuit against deciding patent challenges under the Hatch-Waxman Act's provisions in favor of generics, they ignore the multitude of decisions where the Federal Circuit has done so. *See, supra* at n.14. A Federal Trade Commission survey reported that, in the first 17 years after the Hatch-Waxman Act's enactment, innovator pharmaceutical companies prevailed in only 27 percent of patent challenges (11 out of 40) by generic companies. Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* 20 (July 2002). In innovator appeals of those losses, the Federal Circuit reversed the district court's finding only once. *Id.* at 21.

In sum, four cherry-picked Federal Circuit decisions in addition to the instant case, each affirming a decision reached by the lower court after trial, on the basis of a unique and extensive factual record, do not a "troubling pattern" make.

C. Neither the Text of nor Policy Implications Behind the Hatch-Waxman Act Reflect Congressional Intent to Redefine the Standard for Non-Obviousness in the Context of New Pharmaceuticals

The Petition mistakenly portrays the Hatch-Waxman Act as a one-sided endorsement of the generic industry to justify its request to undermine pharmaceutical compound patent protection. Rather, the Hatch-Waxman Act was a "groundbreaking compromise in the public interest" that *supported* patent protection for pharmaceuticals. Drug Price Competition and Patent Term Restoration Act: S. 2926 before the Senate, 98th Cong. (1984) (Statement by Senator Hatch). According to the Act's sponsor, on the one hand, "[t]he research-based drug industry obtains an *extension of patents* for new drug discoveries" and, on the other hand, "[t]he generic drug industry gets the ability to bring generic copies of off-patent drugs to market *as soon as the patent expires*." *Id.* (emphasis added). With regard to generics, the focus of the Act was to support generic entry *after* patent expiration, with the sponsor of the bill considering challenges to patents like this one "a side issue." Drug Price Competition and Patent Term Restoration Act: Shaw Amendment to Waxman Amendment: 18/30 Month Limitation on FDA Approval of Pending ANDA, before the House, 98th Cong. (1984) (Statement by Congressman Waxman).

With respect to innovator pharmaceutical companies, the purpose of the Hatch-Waxman Act's patent extension was to support "investment and commitment to research and development." Drug Price Competition and Patent Term Restoration Act: S. 2926 before the Senate, 98th Cong. (1984) (Statement by Senator Hatch); *see also*

H.R. Rep. No. 98-857, pt. 1 (June 21, 1984). The Hatch-Waxman Act recognized that, to ensure robust research and development efforts that result in life-saving and life-extending drugs, appropriate pharmaceutical patent protection is crucial. Drug Price Competition and Patent Term Restoration Act: H.R. 3605, before the House, 98th Cong. (1984) (Statement by Congressman Walgren) (Patent term extension "will encourage more research, a goal we should favor in an effort to relieve pain and cure diseases that still plague mankind.").

The precise parameters of the balance struck by Congress are not at issue here. The one thing Congress certainly did not do as part of enacting the Hatch-Waxman Act, however, was to modify the statutory standards of patentability, or suggest that there should be a different, more lenient, standard for adjudicating the obviousness of pharmaceutical compounds. Rather, Congress intentionally left in place a single standard for assessing obviousness for all types of inventions -- that of 35 U.S.C. § 103.

The patent statute prevents precisely the analysis that Petitioners urge this Court to adopt -- one that looks backward, using the invention as a guide to find the "closest prior art." Disregarding the patent statute and this Court's precedent, Petitioners and Amicus propose the following new standard for assessing the obviousness of pharmaceutical compounds:

> [C]hemical compound patent claims should be evaluated on a case-by-case basis, with less focus on "predictability" *per se* of the claimed

> compound and greater focus on whether the claimed compound was "obvious to try" . . . .

Petition at 5; *see also* Petition at 31; Amicus at 17.

According to Petitioners, the consideration of "predictability" should be eliminated "[i]n fields where those of ordinary skill routinely manage unpredictability," in particular, chemical compound inventions -- where the work is difficult, the odds of success are slim, and the need for success is great. Petition at 26.[16] In other words, Petitioners and Amicus argue for a standard that makes it harder to obtain a patent for the most unpredictable and thereby most elusive research areas. This is illogical.

Worse, Petitioners' proposal is directly contrary to the patent statute. Petitioners rely on the process of medicinal chemistry research to denigrate the resulting inventions: "[P]roperties of compounds are tested day after day in the methodical trial-and-error process that is the mainstay of chemical synthesis." Petition at 27. However, under Section 103, "patentability as to this requirement is not to be negatived by the manner in which the invention was made, that is, it is immaterial whether it resulted from long toil and experimentation or from a flash of genius." *Graham*, 383 U.S. at 17 n.7 (quoting Reviser's Note to Section 103); *see also*, *In re Dow Chem. Co.*, 837 F.2d 469, 472 (Fed. Cir. 1988) ("Most technological advance is the fruit of methodical, persistent investigation, as is recognized in *35 U.S.C. § 103* ('Patentability shall not be negatived by the manner in which the invention was made').").

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16. *See Yamanouchi*, 231 F.3d at 1341 ("Of the 11,000 candidates for suitable compounds . . . the FDA approved only four for consumer use."); *In re Mayne*, 104 F.3d at 1343.

Further, Petitioners' proposed elimination of "predictability" from the obviousness inquiry conflicts with years of precedent, including this Court's recent decision in *KSR*.[17] Long-held principles of obviousness that *KSR* found "instructive" focus on predictability: "If a person of ordinary skill can implement a *predictable* variation, § 103 likely bars its patentability"; and "a court must ask whether the improvement is more than the *predictable* use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417 (citing *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co., Inc.*, 396 U.S. 57 (1969)) (emphasis added). In *KSR*, this Court additionally held that obviousness may be found from the need to solve a problem and "a finite number of identified, *predictable* solutions," such that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp" which "leads to the *anticipated* success." *KSR*, 550 U.S. at 421 (emphasis added); *see also Corona Cord Tire Co. v. Dovan Chem., Corp.*, 276 U.S. 358, 369 (1928) (not obvious when "[t]he catalytic action of an accelerator cannot be *forecast* by its chemical composition (emphasis added)).

Finally, while Petitioners term their proposal a "subject-matter sensitive calibration," there is no provision

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17. While Petitoners pay lip service to the concept that obviousness is a fact specific, case-by-case inquiry, the rule of decision they propose instead would simply count the number of atoms that are different (with the full benefit of hindsight) and if the number is small enough simply assume that a research chemist, through trial and error, eventually would have found the patented compound. This is precisely the type of rigid mechanical approach KSR forbids.

in the statute or precedent for different standards based on "subject-matter." As the Federal Circuit's predecessor stated in *In re Papesch*, "[t]he problem of 'obviousness' under Section 103 in determining the patentability of new and useful chemical compounds . . . is not really a problem in chemistry or pharmacology or in any other related field of science such as biology, biochemistry, pharmacodynamics, ecology, or others yet to be conceived. It is a problem of patent law." 315 F.2d 381, 386 (C.C.P.A. 1963). And, the requirement that the question of obviousness be viewed through the eyes of one skilled in the art already provides any necessary "subject-matter calibration." 35 U.S.C. § 103.

D. Petitioners Relied Solely on the "Lead Compound" Analysis Below, and the Present Case Was Decided Correctly on Its Particular Facts

Even if there were a ripe question for this Court to address with respect to the obviousness standard to be applied to pharmaceutical compound patents (and there is not), this case would not be the appropriate vehicle for its resolution. First, throughout the case, Petitioners anchored their obviousness theory on the lead compound analysis and did not raise below the issues they now argue here. Second, what Petitioners really seek is for this Court to review and reverse factual findings made by the district court upon a full and largely undisputed factual record and subsequently affirmed by the Federal Circuit. This Court's certiorari jurisdiction does not exist to provide losing litigants an opportunity to reargue factual issues lost at trial and affirmed on appeal. Third, the courts below followed this Court's precedent, specifically the flexible approach of *KSR* -- and the lead compound framework did not dictate the results.

1. Petitioners Relied on the Lead Compound Analysis as the Sole Basis for Their Obviousness Challenge

Petitioners employed a lead compound analysis as their sole obviousness theory at trial, supported by testimony that those in the field actually approached research in this manner. (App. 58a-59a). On appeal to the Federal Circuit, Petitioners did not challenge whether the lead compound analysis was the correct approach, but rather asserted that the district court erred by applying the analysis incorrectly. Petitioners argued to the Federal Circuit:

> At the very least, this Court should vacate the district court's finding that the compounds of DuPont's '902 patent do not qualify as "lead compounds," and remand the case for the district court to conduct a *proper obviousness analysis starting with those lead compounds.*

(Brief for Appellant at 4, 2009 WL 4088507 at 6) (emphasis added). The Federal Circuit indicated that it understood that Petitioners were challenging the "factual findings underlying the district court's determination." (App. 14a). Only now that both courts below have rejected Petitioners' desired outcome of the lead compound analysis -- the only analysis ever presented by Petitioners below -- do Petitioners assert that the "test" is flawed.[18]

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18. The only issue with the district court's legal analysis that Petitioners raised below was that the '902 patent compounds should be presumed to be leads because, based on a hindsight analysis, those compounds are structurally closest to olmesartan medoxomil. This argument was soundly rejected by the Federal Circuit. (App. 17a). Additionally, Petitioners argued that under

This Court rarely, if ever, considers arguments that were not made below. *Youakim v. Miller*, 425 U.S. 231, 234 (1976) ("Ordinarily, this Court does not decide questions not raised or resolved in the lower court."). If, as Petitioners now contend, the Federal Circuit should consider adopting a new approach to resolving obviousness in pharmaceutical compound cases, the appropriate first step is to ask the Federal Circuit to do so.

2. The Courts Below Rejected Petitioners' Argument of Obviousness on the Factual Record Adduced at Trial

Although couched now as policy arguments, Petitioners' real quarrel remains their disagreement with the factual findings of the courts below. The Petition maintains that choosing the '902 patent compounds and modifying them to reach olmesartan medoxomil should have been regarded as routine for an ordinary chemist in this field. Petition at 26, 28, 31. The courts below decided these *factual* questions in precisely the opposite way. Petitioners' argument here relies on direct contradictions of the facts found by the district court and affirmed by the Federal Circuit:

- **Petitioners' Argument**: the '902 patent compounds were "particularly active" and "showed marked improvement over the previous generation of ARBs." (Petition at 6; Amicus at 18).

Altana, multiple compounds could be leads. The Federal Circuit agreed that multiple compounds could be leads, but the facts demonstrated the '902 compounds were not among them: "[T]he district court selected multiple compounds as leads, just not the compounds disclosed in the '902 patent." (App. 18a).

The Facts: "many of the latter ARBs demonstrated greater potency and all had been more thoroughly studied than the '902 ARBs." (App 16a).

- **Petitioners' Argument**: the invention "differs from one of the compounds disclosed by the '902 patent by *a single atom*" which is a "minor difference" and "routine" modification. (Petition at 7, 28; Amicus at 18).

  The Facts: "[t]his change results in opposing chemical properties" and "is of greater significance than it superficially appears, as it is the difference between functional groups." (App. 62a; App. 22a n.4).

- **Petitioners' Argument**: "addition of a medoxomil [prodrug] group at the 5-position" was "routine" or "plainly obvious." (Amicus at 19; Petition at 7, 28)

  The Facts: "scant evidence" to use a prodrug approach and, even if one did, "little evidence that [an ordinary chemist] would have selected the promoeity medoxomil." (App 68a; App. 69a).

Petitioners' stated view of these "facts" is offered to support a conclusion that "the 'lead compound' test is far too narrow" and "ignores" factual detail.[19] Amicus at 19;

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19. The Amicus brief cites other facts as "undisputed" (Amicus at 18-19). The opinions of the courts below contradict each one of these supposedly undisputed "facts." For example, while the Amicus says that "[t]he 4-position was known to be the only

Petition at 28. But, none of these supposed facts argued in the Petition were established: Rather, the "facts" relied on by Petitioners here were explicitly *rejected* after a ten day trial.

Review of post-trial factual findings, affirmed by the Court of Appeals, and predominantly based on the admissions of the Petitioners' own witnesses, is not a reason for this Court to grant certiorari. "A petition for a writ of certiorari is rarely granted when the asserted error consists of erroneous factual findings or the misapplication of a properly stated rule of law." *Rules of the Supreme Court of the United States* at 6, Rule 10 (Effective Feb. 16, 2010). This Court "cannot undertake to review concurrent findings of fact by two courts below in the absence of a very obvious and exceptional showing of error." *Graver Tank & Mfg. Co. v. Linde Air Prod. Co.*, 336 U.S. 271, 275 (1949) (rule applies with additional force in patent cases where evidence consists largely of expert testimony); *see also United States v. Johnston*, 268 U.S. 220, 227 (1925) ("We do not grant a certiorari to review evidence and discuss specific facts.").

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feasible location where the compound could be modified" (Amicus at 18), the district court found it "illogical to conclude" that a person of ordinary skill would "disregard one of the ['902 patent compounds'] distinguishing characteristics, specifically their increased lipophilicity at the 4-position" and would "alter [that] 'advantageous part' of the '902 patent compounds." (App. 68a; *see also* App. 23a (explicitly quoting and affirming this finding)).

3. The Lower Courts Followed This Court's Precedents and Correctly Found that Olmesartan Medoxomil Was Not Obvious

Under the facts found by the district court after trial, olmesartan medoxomil is not obvious. Both courts below looked to the four-factored factual analysis of *Graham*. *Graham*, 383 U.S. at 17-18; App. 12a; *see also* App. 41a-83a. Both courts heeded this Court's direction in *KSR* that the inquiry must be a flexible one. (App. 13a-14a; 18a) ("In keeping with the flexible nature of the inquiry after *KSR*, the motivation to select and modify a lead compound need not be explicit in the art" and should "not rigidly focus on the selection of a single, best lead compound."); (App. 57a) ("The requisite motivation can come from any number of sources and need not necessarily be explicit in the art.").

The lead compound analysis did not dictate the result in the courts below -- the facts did. Both courts found that Respondents' invention would not be obvious even if the analysis started with the '902 compounds, on grounds that there was no reason (implicit or explicit) to make the modifications necessary to reach olmesartan medoxomil. (App. 15a; App. 22a) ("[Petitioner] failed to show that . . . the skilled artisan would have been motivated to modify the '902 compounds to synthesize olmesartan medoxomil, the claimed invention. . . . Such a holding would have been based on hindsight."); (App. 65a) ("[Petitioner] still fails to prove . . . that a person of ordinary skill in the art would have been motivated to modify the 4- and 5-positions of the '902 patent compounds to derive the invention at issue."). And, both courts below found that the art taught away from the modifications advocated by Petitioner. (App. 21a) ("Thus, the compounds in the prior

art, including the parties' proposed lead compounds, favor lipophilic 4-substituents rather than the 4-hydrophilic group of olmesartan medoxomil."); (App. 45a) ("[T]he Court finds that the prior art taught away from the use of a hydrophilic group at the 4-position of the imidazole ring."). The Petition does not argue that obviousness here may be found without a reasoned basis for modifying the '902 patent compounds in the manner required, or that the extensive factual record of teaching away can be ignored. Nor could it -- *KSR* requires proof of a reason to combine elements and notes that "teaching away" is a prime indication of non-obviousness.

Accordingly, there is no issue for this Court to address here -- only Petitioners' dissatisfaction that the facts disproved the sole theory they chose to advance.

CONCLUSION

The Petition for a writ of certiorari should be denied.

Respectfully submitted,

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